Amphotericin B Emulsion

DESCRIPTION:
Amphotericin B Emulsion is a sterile, yellow, col-oured lipophilic intravenous infusion containing Amphotericin B suspended in an oil-in-water emulsion base.

Amphotericin B is a polyene, antifungal antibiotic produced from a strain of Streptomyces nodosus. Amphotericin B has a molecular weight of 924.10 with a molecular formula of C₃₆H₅₉NO₁₈.

COMPOSITION:
Each mL contains:
Amphotericin B 1 mg, Soybean oil U.S.P., Glycerine I.P., Purified Egg Lecithin, Sodium Hydroxide I.P. and Water for Injection I.P.

THERAPEUTIC INDICATIONS:
Amphotericin B Emulsion is indicated for the treatment of:
- Visceral leishmaniasis (Kala Azar).
- Febrile neutropenia in Cancer Patients.

PRECLINICAL DATA:
In rodents, Amphotericin B is at least 80-fold less toxic than conventional desoxycholate formulation of Amphotericin B when studied for toxicity. Amphotericin B gets distributed rapidly into the reticulo-endothelial System (RES) and hence a rapid build-up of Amphotericin B concentration is achieved in liver and spleen which are the target organs in patients of Visceral leishmaniasis (Kala Azar).

AMPHOMUL was studied for safety and efficacy in visceral leishmaniasis patients infected with Leishmania donovani.

AMPHOMUL achieved high rates of acute parasitic clearance in patients when total doses of 9-15 mg/kg were administered. Most of these patients remained parasitologically free for follow-up periods of 6 months or longer. Efficacy is expressed as both acute parasitic clearance at the end of therapy (EOT) and as overall success (clearance with no relapse) during the follow-up period (F/U) of greater than 6 months for patients.

AMPHOMUL, as an IV infusion over a period of 2 to 4 hours at a dosage of 5 mg/kg body weight showed better efficacy in febrile neutropenic cancer patients with definite/probable/prospective fungal infection. Overall AMPHOMUL had shown favourable outcome in febrile neutropenic cancer patients with definite/probable/prospective fungal infection. Very few breakthroughs in the fungal infection were observed during the study. More than 50% patients survived for 7 days beyond end of therapy.

AMPHOMUL, administered as an IV infusion over a period of 2 to 4 hours at a dosage of 5 mg/kg body weight showed better efficacy in febrile neutropenic cancer patients with definite/probable/prospective fungal infection. Overall AMPHOMUL had shown favourable outcome in febrile neutropenic cancer patients with definite/probable/prospective fungal infection. Very few breakthroughs in the fungal infection were observed during the study. More than 50% patients survived for 7 days beyond end of therapy.

In an open label multi-center trial, the efficacy of AMPHOMUL (5 mg/kg/day) was evaluated for the empirical treatment of 40 adult and pediatric neutropenic patients who were febrile despite having received at least 96 hours of broad spectrum antibacterial therapy. Therapeutic success required (a) resolution of fever during the neutropenic period, (b) absence of an emergent fungal infection, (c) patient survival for at least 7 days post therapy, (d) no discontinuation of therapy due to toxicity or lack of efficacy, and (e) resolution of any study-entry fungal infection.

AMPHOMUL, administered as an IV infusion over a period of 2 to 4 hours at a dosage of 5 mg/kg body weight showed better efficacy in febrile neutropenic cancer patients with definite/probable/prospective fungal infection. Overall AMPHOMUL had shown favorable outcome in febrile neutropenic cancer patients with definite/probable/prospective fungal infection. Very few breakthroughs in the fungal infection were observed during the study. More than 50% patients survived for 7 days beyond end of therapy.

The study demonstrated efficacy and safety of AMPHOMUL in the treatment of febrile neutropenia. Overall AMPHOMUL emulsion was well tolerated with very low incidence of nephrotoxicity and infusion related AEs.

The summary of all the four studies are as follows:

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Study Code</th>
<th>Number of Subjects</th>
<th>Treatment Arms</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>ESB/AM/12/002 (Kala Azar)</td>
<td>48</td>
<td>2 MKD x 7 days, 2.5 MKD x 4 alternate days</td>
<td>The drug showed good tolerability.</td>
</tr>
<tr>
<td>2.</td>
<td>ESB/AM/12/003 (Kala Azar)</td>
<td>45</td>
<td>1 MKD x 3 days, 3 MKD x 3 days</td>
<td>Nearly 100% apparent cure rate.</td>
</tr>
<tr>
<td>3.</td>
<td>ESB-AM/BE-1202 (Febrile Neutropenia)</td>
<td>40</td>
<td>5 MKD x 28 days (maximum)</td>
<td>The study demonstrated efficacy and safety of AMPHOMUL in the treatment of febrile neutropenia. Overall AMPHOMUL, emulsion was well tolerated with very low incidence of nephrotoxicity and infusion related AEs.</td>
</tr>
<tr>
<td>4.</td>
<td>ESB-AM/BE-KA-0909 (Kala Azar)</td>
<td>50</td>
<td>7.5 mg/kg on Day 1 and Day 2</td>
<td>Apparent cure 100%</td>
</tr>
<tr>
<td>5.</td>
<td>ESB-AM/BE-KA-0908 (Kala Azar)</td>
<td>50</td>
<td>7.5 mg/kg on Day 1 and Day 2</td>
<td>Definitive cure 93.33%</td>
</tr>
</tbody>
</table>

MKD mg/kg/day.
DOSEAGE AND ADMINISTRATION:

Dosage:
The recommended daily dosage for adults and children is 5 mg/kg given as a single infusion, administered intravenously at a rate of about 2.5 mg/kg/hour.

For Kala Azar:
The recommended total dose for adults and children for the treatment of Visceral Leishmaniasis (Kala Azar) is 15mg/kg and can be administered in any one of the following dosing regimens:
1. A single dose of 10mg/kg/day administered over a period of 4 hours (not recommended for children below 5 years of age)
2. A dose of 5mg/kg/day on three alternate days.
3. A dose of 7.5mg/kg/day on two alternate days.

For Febrile neutropenia:
The recommended dose is 5 mg/kg/day.

Administration:
AMPHOMUL should always be mixed with 5% Dextrose Injection and administered as an infusion mixture. The recommended concentration for intravenous infusion is 0.5 mg/mL to 1 mg/mL.

Preparation of infusion mixture - Shake the vial gently and withdraw the contents from the vials into one or more 10 / 20ml syringes using 18 gauge needle. Purge the needle from each syringe filled with AMPHOMUL. Attach to the syringe the 5µ syringe filters provided with each vial pack and then fit the 18 gauge needle to the other end of the syringe filter. Insert the needle into an I.V. bag containing 5% Dextrose Injection and empty the contents of the syringe into the bag. Shake the bag until the contents are thoroughly mixed.

Do not use the infusion mixture if there is any visible evidence of foreign matter.

Aseptic technique must be strictly observed throughout handling of AMPHOMUL, since no preservative is present in AMPHOMUL.

AMPHOMUL vials are for single use and hence any unused product should be discarded from the used vials.

DO NOT DILUTE AMPHOMUL WITH SODIUM CHLORIDE INJECTION (SALINE) OR MIX WITH OTHER DRUGS OR ELECTROLYTES.

DO NOT USE AN ON-LINE MICROBIAL FILTER (0.2µ Pore Size).

DURING ADMINISTRATION OF AMPHOMUL MIXTURE FOR INFUSION, GENTLY SHAKE THE CONTENTS OF THE INFUSION BAG EVERY ONE HOUR FOR PROPER MIXING.

IT IS NOT ADVISABLE TO STORE AMPHOMUL MIXTURE FOR INFUSION.

During administration of AMPHOMUL, serum creatinine level should be measured to monitor the renal toxicity. Dose adjustments should be made only after taking into account the overall clinical condition of the patient.

CONTRA-INDICATIONS:
AMPHOMUL is contra-indicted in patients who have shown hypersensitivity to Amphotericin B or any other component included in the formulation.

WARNINGS:
Anaphylaxis has been reported with the administration of Amphotericin B containing preparations. If severe respiratory distress occurs the infusion should be immediately discontinued and the patient should not receive further infusions of AMPHOMUL.

PRECAUTIONS:
AMPHOMUL should be administered under close clinical observation. Fever and chills may occur 1-2 hours after administration of AMPHOMUL.

Amphotericin B is known to cause sometimes hyperproteinemia, respiratory stirker and modest hypotension. True bronchospasm or anaphylaxis is rare. As a precautionary measure, a test dose of AMPHOMUL equivalent to 1 mg of Amphotericin B is always recommended to be infused slowly. The patients should be observed for 2 hours prior to infusing the usual therapeutic dose.

Serum creatinine should be monitored during AMPHOMUL therapy. It is also advisable to regularly monitor liver function, blood count and serum magnesium and potassium content.

DRUG INTERACTIONS:
Amphotericin B is known to interact with the following drugs, which should be thus administered with caution.

Since nephrotoxic effects may be additive, the concomitant or sequential use of AMPHOMUL and other drugs with similar toxic potential (e.g., aminoglycosides, capreomycin, colistin, ciprofloxacin, metronidazole, penicillins, polymyxin B, vancomycin) should be avoided, if possible. Intensive monitoring of renal function is recommended. If AMPHOMUL is used concomitantly with any of the known nephrotoxic drugs, AMPHOMUL may potentiate the effects of skeletal muscle relaxants due to hypokalemia.

PREGNANCY AND LACTATION:
AMPHOMUL should only be used during pregnancy or breast feeding if the possible benefits to be derived outweigh the potential risks involved.

It is not known if AMPHOMUL is excreted in human milk.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
The clinical condition of most patients treated with AMPHOMUL precludes driving vehicles or operating machinery.

UNDESIRABLE EFFECTS:
Fever and chills / rigors are the most commonly experienced infusion related reactions expected to occur during administration of AMPHOMUL, when no premedication to prevent these reactions is provided. AMPHOMUL treated patients experienced a significantly lower incidence of infusion-related reactions.

OVERDOSE:
If overdose occurs, stop administration of AMPHOMUL immediately. Carefully monitor clinical symptoms, monitor renal and hepatic function, serum electrolytes and hematological parameters.

AMPHOMUL has a large safety margin over the clinical dosage recommended. However, the toxicity of AMPHOMUL due to overdose has not been studied.

INCOMPATIBILITIES:
AMPHOMUL should not be co-administered through the same I.V. catheter with blood or plasma; although the clinical significance is not known. In-vitro studies have shown that the globular component of the emulsion vehicle forms aggregates when it comes in contact with human plasma.

AMPHOMUL is incompatible with saline solution and other solutions containing electrolytes.

STORAGE CONDITIONS:
Intact vials of AMPHOMUL should be stored below 25°C, do not freeze and protect from direct exposure to light. Any unused material should be discarded.

PRESENTATION:
AMPHOMUL is available in single use 10ml vials containing 50 mg Amphotericin B. Each vial pack is provided with 5µ syringe filter and package insert.